FORM PTO-1390 (Modified) (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
4440	09/868586

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/10358	December 23, 1999	December 23, 1998

TITLE OF INVENTION
CYCLOSPORIN SOLUTION

APPLICANT(S) FOR DO/EO/US
Wilfried FISCHER

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
    A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☒ Certificate of Mailing by Express Mail
19. ☒ Other items or information:

1. Specification and claims;
2. Information Sheet
3. The fee calculation must be based upon the claims as amended and added in the attached Preliminary Amendment.

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/868586	PCT/EP99/10358	4440

20. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		CALCULATIONS PTO USE ONLY
☒ Search Report has been prepared by the EPO or JPO	$860.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482)	$670.00	
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	$760.00	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO	$970.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$96.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =	860.	00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	17 - 20 =	0	x $18.00		
Independent claims	1 - 3 =	0	x $78.00		
Multiple Dependent Claims **(check if applicable)**.			☐		
TOTAL OF ABOVE CALCULATIONS =				860.	00
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**.			☐		
SUBTOTAL =				860.	00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+		
TOTAL NATIONAL FEE =				860.	00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable)**.			☐		
TOTAL FEES ENCLOSED =				860.	00
				Amount to be: refunded	$
				charged	$

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. 01-1944 in the amount of $860.00 to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 01-1944 A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

Eugene Lieberstein
NAME

24,645
REGISTRATION NUMBER

June 20, 2001
DATE

SCANNED, # 12

EXPRESS MAIL CERTIFICATE OF MAILING - SEPARATE PAPER

IN THE MATTER OF: Wilfried FISCHER

ATTORNEY'S DOCKET NO.: 4440

FOR: CYCLOSPORIN SOLUTION

I hereby certify that the new PCT/DO application with:

X transmittal letter

X specification and claims

____ declaration

X Preliminary Amendment

X Information Sheet

is being deposited with the United States Postal Services "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated below and is addressed to Assistant Commissioner for Patents, BOX PCT, Washington, DC 20231

on June 20, 2001.

EXPRESS MAIL LABEL NO.

EL179653242US

Anne R. Jacoby
(Name of person making deposit)

Anne R. Jacoby
(Signature)

June 20, 2001
(Date)

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1251 Avenue of the Americas
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1-212-278-1000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN THE MATTER OF:

Wilfried FISCHER

ORDER NO.:4440

FOR: CYCLOSPORIN SOLUTION

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
& Trademarks
Washington, DC 20231

S I R:

It is requested that the application be amended as follows.

IN THE CLAIMS

Attached please find a copy of amended claims 1, 3, 4, 6-11 and 15-16 and new claim 17 as follows. A clean copy of claims 1-17 is also attached.

REMARKS

The claims have been amended to eliminate multiple dependencies.

Claims 1and 3 have been amended to delete the term "or a mixture of nonionic surfactants" as the term "nonionic surfactant" in the claim is inclusive of mixtures of nonionic surfactants. Claim 17 sets out the claim to dependent mixtures in claim 1 is a dependent claim.

Respectfully submitted,

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IN THE CLAIMS

1. (Amended) Cyclosporin solution comprising dexpanthenol, an anionic surfactant and a nonionic surfactant [or a mixture of nonionic surfactants].

3. (Amended) Cyclosporin solution according to claim 1 [either of the preceding claims,] where the solution comprises 0.2-2 parts by weight of dexpanthenol, 0.2-1 part by weight of anionic surfactant and 0.5-6 parts by weight of nonionic surfactant [or a mixture of nonionic surfactants] per part by weight of cyclosporin.

4. (Amended) Cyclosporin solution according to claim 1 [any of the preceding claims,] which additionally comprises a diluent.

6. (Amended) Cyclosporin solution according to claim 4 [or 5,] in which diluent is ethanol.

7. (Amended) Cyclosporin solution according to claim 1 [any of the preceding claims,] in which the anionic surfactant is sodium lauryl sulfate.

8. (Amended) Cyclosporin solution according to claim 1 [any of the preceding claims,] in which the nonionic surfactants are polysorbate 80 and glycerol-polyethylene glycol oxystearate.

9. (Amended) Cyclosporin solution according to claim 1 [any of Claims 4-8,] consisting of about 11% by weight of cyclosporin A, about 11% by weight of dexpanthenol, about .5.6% by weight of anionic surfactant, about 55.6% by weight of a mixture of nonionic surfactants and about 16.8% by weight of a diluent, in particular ethanol.

10. (Amended) Cyclosporin solution according to claim 1 [any of Claims 4-8,] consisting of about 19-26% by weight of cyclosporin A, about 8-10% by weight of dexpanthenol, about 8-10% by weight of anionic surfactant, about 44-50% by weight of nonionic surfactant and about 12-14% by weight of a diluent.

11. (Amended) Oral pharmaceutical comprising a solution according to claim 1 [any of Claims 1-10].

15. (Amended) Use of a solution according to claim 1 [any of Claims 1-10] for producing a stable aqueous colloidal cyclosporin solution.

16. (Amended) Use of a solution according to claim 1 [any of Claims 1-10] for producing an oral pharmaceutical for immunosuppression

NEW CLAIM

17. (New) The cyclosporin solution of claim 1 wherein the nonionic surfactant is a mixture of nonionic surfactants.

Patent Claims

1. Cyclosporin solution comprising dexpanthenol, an anionic surfactant and a nonionic surfactant.

2. Cyclosporin solution according to claim 1, in which the cyclosporin is cyclosporin A.

3. Cyclosporin solution according to claim 1 where the solution comprises 0.2-2 parts by weight of dexpanthenol, 0.2-1 part by weight of anionic surfactant and 0.5-6 parts by weight of nonionic surfactant per part by weight of cyclosporin.

4. Cyclosporin solution according to claim 1 which additionally comprises a diluent.

5. Cyclosporin solution according to claim 4, in which the diluent content is 10-40% by weight based on the total weight of the solution.

6. Cyclosporin solution according to claim 4 in which diluent is ethanol.

7. Cyclosporin solution according to claim 1 in which the anionic surfactant is sodium lauryl sulfate.

8. Cyclosporin solution according to claim 1 in which the nonionic surfactants are polysorbate 80 and glycerol-polyethylene glycol oxystearate.

9. Cyclosporin solution according to claim 1 consisting of about 11% by weight of cyclosporin A, about 11% by weight of dexpanthenol, about .5.6% by weight of anionic surfactant, about 55.6% by weight of a mixture of nonionic surfactants and about 16.8% by weight of a diluent, in particular ethanol.

10. Cyclosporin solution according to claim 1 consisting of about 19-26% by weight of cyclosporin A, about 8-10% by weight of dexpanthenol, about 8-10% by weight of anionic surfactant, about 44-50% by weight of nonionic surfactant and about 12-14% by weight of a diluent.

11. Oral pharmaceutical comprising a solution according to claim 1.

12, Pharmaceutical according to claim 11, where the solution is used to fill capsules.

13. Pharmaceutical according to claim 12, where the capsules are soft gelatin capsules.

14. Pharmaceutcial according to claim 11, where the solution is in the form of an oral solution.

15. Use of a solution according to claim 1 for producing a stable aqueous colloidal cyclosporin solution.

16. Use of a solution according to claim 1 for producing an oral pharmaceutical for immunosuppression

17. The cyclosporin solution of claim 1 wherein the nonionic surfactant is a mixture of nonionic surfactants.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. :

U.S. National Serial No. :

Filed :

PCT International Application No. : PCT/EP99/10358

VERIFICATION OF A TRANSLATION

I, Susan POTTS BA ACIS

Director to RWS Group plc, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare:

That the translator responsible for the attached translation is knowledgeable in the German language in which the below identified international application was filed, and that, to the best of RWS Group plc knowledge and belief, the English translation of the international application No. PCT/EP99/10358 is a true and complete translation of the above identified international application as filed.

I hereby declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application issued thereon.

Date: June 1, 2001

Signature of Director :

For and on behalf of RWS Group plc

Post Office Address : Europa House, Marsham Way,
Gerrards Cross, Buckinghamshire,
England.

Cyclosporin solution

The present invention relates to a cyclosporin solution.

Cyclosporins are a known group of cyclic undecapeptides. Cyclosporin A ($C_{62}H_{111}N_{11}O_{12}$, molecular weight 1202) is used as immunosuppressant pharmaceutical for the treatment of tissue rejection reactions or excessive immunological responses of the body and is commercially available for example as Sandimmun® and Neoral®. Besides cyclosporin A, a number of additional metabolites are known (cyclosporins B-Z), which show a close relationship to cyclosporin A, both structurally and in some cases also in terms of effect.

The international nonproprietary name of a cyclosporin used for immunosuppression is ciclosporin.

It is additionally known that cyclosporin A has very poor solubility in water. This gives rise to problems in formulating pharmaceutical preparations of cyclosporin A which can be effectively and rapidly absorbed, because rapid and complete or virtually complete absorption of the active ingredient is an indispensible prerequisite for reliable efficacy for the vital indications such as suppression of tissue rejection after organ transplants. Numerous attempts have been made in the prior art to provide cyclosporin A in a formulation which can be absorbed effectively. Because of the great lipophilicity of cyclosporin A, pharmaceutical compositions have been formulated with conventional solid and liquid pharmaceutical carriers, but these often displayed disadvantages, such as inadequate adsorption (Cavanak and Sucker, Formulation of Dosage Forms, Prog. Allergy, 38, 65-72 (1986)), poor tolerability or physical instabilities such as crystallization of the active ingredient. It has also proved to be a disadvantage that the solubility of the active ingredient in the

preparation is often low (about 3%), which means that the amount taken for a daily dose of up to 1 g of cyclosporin A is up to 30 g of the formulation.

The patent DE 29 07 460 discloses, for improving the storage and absorption of cyclosporin A, the use of a carrier composed of a polyalkylene glycol triglyceride, of a fatty acid triglyceride and of a monoglyceride or diglyceride. The formulation is used as oral solution, injection solution or capsule contents. Ethanol can be added to promote solubility. The absorption of such as solution is relatively good, but it has the disadvantage that the blood level may vary greatly and depends on food intake.

An improved formulation is described in DE 39 30 928 as so-called microemulsion preconcentrate, which consists of a hydrophilic phase, a lipophilic phase and an emulsifier. The hydrophilic component may be C_{1-5}-alkyl or tetrahydrofurfuryl diether or a partial ether of low molecular weight mono- or polyoxyalkanediols or 1,2-propylene glycol. The lipophilic component may be a medium chain-length triglyceride. A polyethoxylated vegetable oil, for example, is provided as emulsifier.

In a comparative absorption study on beagle dogs there was found to be a 49% improvement in absorption compared with the formulation disclosed in DE 29 07 460.

DE 195 21 974 describes a solution of cyclosporin A in a mixture of an emulsifying vitamin E derivative, another emulsifier, such as a polyoxyethylene vegetable oil ester and ethanol. The formulation shows a profile of blood levels in beagle dogs comparable to the formulation of DE 39 30 928.

WO 97/35603 describes a microdispersion comprising amorphous cyclosporin A, lower alkanols and polyoxyalkylene emulsifiers as cosolvents.

WO 97/07787 discloses a cyclosporin formulation which comprises an alkanol solvent with 2 to 3 carbon atoms and an emulsifier selected from polyoxyethylene alcohols and fatty acid monoesters of ethoxylated C_{4-6}-polyols.

There continues to be a need for a reasonably priced, well tolerated and stable cyclosporin preparation which, in particular, is easy to produce, is readily miscible with water and forms a stable cyclosporin solution therein, which ensures good absorption of the cyclosporin on oral administration, and which can contain cyclosporin in high concentration.

One object of the present invention is thus to provide a cyclosporin preparation which displays the aforementioned advantages.

It has now been found, surprisingly, that colloidal solutions which are stable in water and which can be diluted with water as desired without precipitation of cyclosporin are formed from a solution of cyclosporin in exclusively water-miscible excipients only in combination with dexpanthenol, an anionic surfactant and a nonionic surfactant or a mixture of nonionic surfactants. Bioavailability investigations have shown good absorption of the active ingredient after oral administration.

The cyclosporin solution according to the invention is able to take up a larger amount of active ingredient per ml of solution than known for cyclosporin formulations in the prior art.

The present invention thus relates to a cyclosporin solution comprising dexpanthenol, an anionic surfactant and a nonionic surfactant or a mixture of nonionic surfactants.

Dexpanthenol is the short name for D-(+)-2,4-dihydroxy-N-(3-hydroxypropyl)-3,3-dimethylbutyramide.

The preferred cyclosporin is cyclosporin A.

The cyclosporin solution according to the invention may contain the active ingredient plus dexpanthenol, the anionic surfactant and the nonionic surfactant and, where appropriate, other pharmaceutically acceptable excipients in any desired amount as long as the amount of dexpanthenol, of the anionic surfactant and of the nonionic surfactant is sufficient to form a stable cyclosporin solution. The solution preferably comprises 0.2-2 parts by weight of dexpanthenol, 0.2-1 part by weight of anionic surfactant and 0.5-6 parts by weight of nonionic surfactant or a mixture of nonionic surfactants per part by weight of cyclosporin.

The cyclosporin solution according to the invention generally comprises 0.2-2, preferably 0.5-2, for example 0.7-1.3, parts by weight of dexpanthenol, 0.2-1, preferably 0.3-0.7, parts by weight of anionic surfactant and 0.5-6, preferably 3-5, parts by weight of nonionic surfactant or a mixture of nonionic surfactants per part by weight of cyclosporin.

The cyclosporin solution according to the invention may advantageously additionally comprise a diluent. The diluent reduces the viscosity of the solution. This had the advantage that when the solution is used to fill, for example, soft gelatin capsules, after intake of the capsule the contents escape very rapidly from the opening capsule, and thus good absorption of the active ingredient is ensured.

In the case of an oral solution which is diluted in water before administration so that its viscosity is reduced very greatly it is possible to dispense with addition of diluent.

If the solution according to the invention is to contain a diluent, the content thereof is advantageously 10-40% by weight, in particular about 20% by weight, based on the total weight of the solution. The preferred diluent is ethanol.

The anionic surfactant which can be used for the solution according to the invention is any conventional pharmaceutically acceptable anionic surfactant. It is also possible to use both an anionic surfactant alone or a mixture of two or more anionic surfactants. Examples of anionic surfactants which can be used according to the invention are alkyl ether sulphates and alkane sulphonates. The preferred anionic surfactant is sodium lauryl sulphate.

The nonionic surfactant which can be used for the solution according to the invention is any conventional, pharmaceutically acceptable nonionic surfactant. It is also possible to use both a nonionic surfactant alone or mixed with other nonionic surfactants, and a mixture of nonionic surfactants is preferred. Examples of nonionic surfactants which can be used according to the invention are glycerol-polyethylene glycol oxystearate (for example Cremophor RH 40), ethoxylated hydrogenated castor oil and polysorbate 80, a polyoxyethylene (80) sorbitan monooleate which is obtainable under the proprietary name Tween 80. The preferred nonionic surfactants are polysorbate 80 and glyerol-polyethylene glycol oxystearate.

A preferred solution according to the invention consists of about 11% by weight of cyclosporin A, about 11% by weight of dexpanthenol, about 5.6% by weight of anionic surfactant, about 55.6% by weight of a mixture of nonionic surfactants, and about 16.8% by weight of diluent, in particular ethanol. This solution is particularly suitable for filling soft gelatin capsules because, owing to its low viscosity, it escapes very rapidly from the opening capsule and ensures good absorption of the active ingredient. Another preferred solution according to the invention consists of about 19-26% by weight of cyclosporin A, about 8-10% by weight of dexpanthenol, about 8-10% by weight of anionic surfactant, about 44-50% by weight of nonionic surfactant and about 12-14% by weight of a diluent.

The combination of dexpanthenol, an anionic surfactant and a nonionic surfactant as solvents for cyclosporin makes available a cyclosporin solution which is readily miscible with water to form a stable aqueous colloidal solution which can be diluted with water as desired without precipitation of cyclosporin. The solution according to the invention is not a microemulsion or microemulsion concentrate and consists exclusively of known pharmaceutical substances. It can be both used to fill capsules and administered in the form of a pleasant-tasting oral solution to the patient.

Compared with the prior art, it was possible owing to the combination of the substances mentioned to dispense with a lipophilic component, which is necessary to form a microemulsion. Completely unexepectedly, dexpanthenol in this case assumes the role of a solubilizer, although it is not a surfactant, resulting in a stable colloidal solution of the cyclosporin in the dissolving medium. The anionic and nonionic surfactants present in the formulation are unable, either alone or in combination, to dissolve the cyclosporin without precipitation.

The surprisingly good dissolving properties of dexpanthenol make it possible to increase the cyclosporin concentration in the solution according to the invention compared with the prior art, so that, for example, an increased concentration of active ingredient can be achieved in pharmaceuticals, or the amount of solution to be administered can be reduced. It is thus possible to produce, for example, smaller capsules which can be taken more easily by the patient.

The present invention thus also relates to an oral pharmaceutical which comprises a cyclosporin solution described above.

Such a pharmaceutical preferably comprises capsules filled with the solution. Soft gelatin capsules are particularly preferred. On examination of the rate of dissolution in media of various pH values as are typical of the gastrointestinal tract, there was found to be substantially pH-independent release of active ingredient from the capsules.

In another embodiment, the pharmaceutical comprising the solution according to the invention is in the form of an oral solution which, besides the cyclosporin solution according to the invention, may contain other conventional, pharmaceutically acceptable additives and, for example, flavourings and colourings and which can be diluted, for example with water, to the required concentration before intake thereof. The cyclosporin solution according to the invention is thus also suitable for easy production of a stable aqueous pleasant-tasting oral solution which can easily be administered to the patient.

The necessary cyclosporin levels in the blood are reached very rapidly and reliably after administration of a pharmaceutical according to the invention, and the

uniformity of the levels in the blood is greater than after administration of the commercially available product Neoral®.

The described solution can be administered in the form of a diluted aqueous solution for intake or as a single-dose drug form, for example in the form of a capsule. A capsule may contain, for example, a single dose of 100 mg of cyclosporin.

A preferred embodiment of the pharmaceutical according to the invention accordingly comprises soft gelatin capsules which each contain a solution according to the invention composed of about 100 mg of cyclosporin A, about 100 mg of dexpanthenol, about 50 mg of sodium lauryl sulphate, about 100 mg of polysorbate 80, about 400 mg of glycerol-polyethylene glycol oxystearate and about 150 mg of ethanol.

The pharmaceutical according to the invention is particularly suitable for immunosuppression.

The following examples are intended to explain the present invention in detail.

Example 1

This example shows the production of a cyclosporin solution according to the invention and of a pharmaceutical according to the invention in the form of soft gelatin capsules.

Soft gelatin capsules with a filling of the following composition were produced:

Cyclosporin A	100 mg
Dexpanthenol	100 mg
Sodium lauryl sulphate (anionic surfactant)	50 mg
Polysorbate 80 (nonionic surfactant)	100 mg
Glycerol-polyethylene glycol oxystearate (nonionic surfactant)	400 mg
Ethanol (diluent)	150 mg

The cyclosporin A was dissolved in ethanol. Separately from this, sodium lauryl sulphate, dexpanthenol, polysorbate 80 and glycerol polyethylene glycol oxystearate were heated gently to produce a clear solution. The two solutions were mixed homogeneously and then used to fill soft gelatin capsules.

Example 2

An absorption study was carried out on six beagle dogs with the capsules produced in Example 1. Each dog was given a 100 mg cyclosporin A capsule in a crossover test comparing with Neoral® (composition: cyclosporin A, ethanol, glycerol, corn oil mono-di-tri-glycerides, propylene glycol, macrogol-glycerol hydroxystearate, alpha-tocopherol) and blood samples were taken after 0.5, 1.0, 1.5 and 2.0 hours. The cyclosporin A levels in the samples of blood taken were determined using a commercially available enzyme immunoassay. The following table indicates in each case the means with standard deviations resulting from the curves of levels in the blood.

Table

Product	Level in the blood ng/ml	Standard deviation ng/ml
Neoral		
0.5 h	457.92	337.28
1.0 h	1222.83	406.48
1.5 h	1616.67	393.71
2.0 h	1432.33	243.08
Test formulation		
0.5 h	435.67	332.11
1.0 h	1201.5	328.79
1.5 h	1398.17	239.36
2.0 h	1170.67	111.88

The example shows that the necessary levels in the blood are reached very rapidly and reliably after administration of the cyclosporin solution according to the invention in the form of a capsule, and the uniformity of the levels in the blood is greater than after administration of the comparison product.

Example 3

A cyclosporin solution of the following composition was produced:

Ingredients

Ciclosporin A	175 mg	(about	19.5%)
Dexpanthenol	80 mg	(about	8.9%)
Sodium lauryl sulphate (anionic surfactant)	80 mg	(about	8.9%)
Polysorbate 80	-		
Glycerol-polyethylene glycol stearate	445 mg	(about	49.4%)
Diluent	120 mg	(about	13.3%)
Total	900 mg		

Example 4

A cyclosporin solution of the following composition was produced;

Ingredients

Ciclosporin A	228 mg	(about	25.3%)
Dexpanthenol	75 mg	(about	8.4%)
Sodium lauryl sulphate (anionic surfactant)	75 mg	(about	8.4%)
Polysorbate 80	-		
Glycerol-polyethylene glycol stearate	410 mg	(about	45.5%)
Diluent	112 mg	(about	12.4%)
Total	900 mg		

Patent Claims

1. Cyclosporin solution comprising dexpanthenol, an anionic surfactant and a nonionic surfactant or a mixture of nonionic surfactants.

2. Cyclosporin solution according to Claim 1, in which the cyclosporin is cyclosporin A.

3. Cyclosporin solution according to either of the preceding claims, where the solution comprises 0.2-2 parts by weight of dexpanthenol, 0.2-1 part by weight of anionic surfactant and 0.5-6 parts by weight of nonionic surfactant or a mixture of nonionic surfactants per part by weight of cyclosporin.

4. Cyclosporin solution according to any of the preceding claims, which additionally comprises a diluent.

5. Cyclosporin solution according to Claim 4, in which the diluent content is 10-40% by weight based on the total weight of the solution.

6. Cyclosporin solution according to Claim 4 or 5, in which the diluent is ethanol.

7. Cyclosporin solution according to any of the preceding claims, in which the anionic surfactant is sodium lauryl sulphate.

8. Cyclosporin solution according to any of the preceding claims, in which the nonionic surfactants are polysorbate 80 and glycerol-polyethylene glycol oxystearate.

9. Cyclosporin solution according to any of Claims 4-8, consisting of about 11% by weight of

cyclosporin A, about 11% by weight of dexpanthenol, about 5.6% by weight of anionic surfactant, about 55.6% by weight of a mixture of nonionic surfactants and about 16.8% by weight of a diluent, in particular ethanol.

10. Cyclosporin solution according to any of Claims 4-8, consisting of about 19-26% by weight of cyclosporin A, about 8-10% by weight of dexpanthenol, about 8-10% by weight of anionic surfactant, about 44-50% by weight of nonionic surfactant and about 12-14% by weight of a diluent.

11. Oral pharmaceutical comprising a solution according to any of Claims 1-10.

12. Pharmaceutical according to Claim 11, where the solution is used to fill capsules.

13. Pharmaceutical according to Claim 12, where the capsules are soft gelatin capsules.

14. Pharmaceutical according to Claim 11, where the solution is in the form of an oral solution.

15. Use of a solution according to any of Claims 1-10 for producing a stable aqueous colloidal cyclosporin solution.

16. Use of a solution according to any of Claims 1-10 for producing an oral pharmaceutical for immunosuppression.

Docket No.
4440

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

CYCLOSPORIN SOLUTION

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on **June 20, 2001** as United States Application No. or PCT International Application Number **09/868,586**

and was amended on _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
198 59 910.2	**Germany**	**23 12 1998**	☐
(Number)	(Country)	(Day/Month/Year Filed)	
PCT/EP99/10358		**23 12 1999**	☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

Michael N. Meller - Registration No. 20,779
Eugene Lieberstein - Registration No. 24,645

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Second inventor's signature	Date
Residence	
Citizenship	
Post Office Address	